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LIVER TRANSPLANTATION FOR IATROGENIC BILE DUCT INJURY DURING CHOLECYSTECTOMY: A FRENCH RETROSPECTIVE MULTICENTER STUDY

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Abbreviations

CHA: Common Hepatic Artery

CMV: Cytomegalovirus

ERCP: Endoscopic Retrograde Cholangiopancreatography

BDI: Bile Duct Injury

MELD: Model for End-Stage Liver Disease

LT: Liver Transplantation

PV: Portal Vein

RHA: Right Hepatic Artery

TIPS: Transjugular Intrahepatic Portosystemic Shunt

Abstract

BACKGROUND : Major bile duct injuries (BDI) following cholecystectomy requires complex reconstructive surgery. The aim was to collect the liver transplantations (LT) performed in France for major BDI following cholecystectomy, to analyze the risk factors and to report the results.

METHODS : National multicenter observational retrospective study. All the patients who underwent a LT in France between 1994 and 2017, for BDI following cholecystectomy, were included.

RESULTS : 30 patients were included. 25 BDI occurred in non hepato-biliary expert centers, 20 were initially treated in these centers. Median time between injury and LT was 3 years in case of an associated vascular injury (11 injuries), versus 11.7 years without vascular injury ($p=0.006$). Post-transplant morbidity rate was 86.7%, mortality 23.5% at 5 years. **DISCUSSION :** Iatrogenic BDI remains a real concern with severe cases, associated with vascular damages or leading to cirrhosis, with no solution but LT. It is associated with high morbidity and not optimal results. This enlightens the necessity of early referral of all major BDI in expert centers to prevent dramatic outcome. Decision to perform transplantation should be taken before dismal infectious situations or biliary cirrhosis and access to graft should be facilitated by Organ Sharing Organizations.

INTRODUCTION

Cholecystectomy is a common surgical procedure, with 116 000 procedures carried out in France in 2017 (1). Iatrogenic bile duct injury (BDI) is a rare, but serious complication of cholecystectomy. Iatrogenic BDI is defined as accidental damage to the biliary tree during surgery, and may be identified during or after the procedure based on biliary leak or obstruction, including cystic stump leaks. The presence and localization of associated vascular injury is important to identify(2,3), although its prognostic significance is debated in the literature(4–6). While most BDI cases are treated without sequelae, major BDI generally requires complex reconstructive surgery, including repair and reconstruction of the biliary system, hepatectomy or, in rare cases, liver transplantation (LT).

The aim of our study was to review the LT performed in France for major iatrogenic BDI following cholecystectomy, the risk factors for adverse outcomes, and to make recommendations for the management of these patients.

METHODS

We conducted a national multicenter observational retrospective study, across all French centers performing, between 1994 and 2017. All patients treated for iatrogenic BDI following cholecystectomy were eligible for participation.

The study summary was sent to each French LT center prior to commencing the project. For each participating center, unique corresponding number was created. This enabled the secure transfer of relevant patient data, including hospital reports, operative and histopathological reports, relevant imaging and other appropriate documents. Data handling and analysis was carried out centrally, at the coordinating center, by a dedicated study coordinator.

Data were collected on gender, age at cholecystectomy, age at LT, indication of cholecystectomy, surgical approach, expert or non-expert center (for cholecystectomy and BDI management with an expert center being defined as a high-volume center familiar with reconstructive hepatobiliary surgery), diagnosis of BDI, delay of BDI diagnosis, type of BDI using Strasberg(7) classification, presence of associated vascular injury, average time between BDI and first treatment, number of surgeries per patient between BDI and LT, usage of endoscopy, usage of interventional radiology, median time between BDI and enrolment onto the LT waiting list, waiting time before LT, median time between BDI and LT, median MELD score, involvement of an expert component, indication of LT, re-transplantation, morbidity post-LT, early graft loss, and overall graft and patient survival.

Expert component is a derogation delivered by French Organ Sharing Organization, to allow a patient to have a LT with a low MELD score. Those patients, to access grafts, need a special prioritization as MELD score exceptions, since their MELD is low and do not reflect the severity of the situation. In France, an “expert component” has to be delivered by the French Organ Sharing Organization after evaluation by two independent transplant experts.

Study end points were perioperative 30-day mortality and graft and patient survival.

All data related to LT is registered, a priori, in the National French transplant database, therefore individual institutional ethic approval is not required.

Statistical analysis

Data collection and statistical analysis were performed using XLSTAT software (Addinsoft) and Microsoft Office Excel 2013 software. Data were expressed as absolute values and percentages for ordinal variables; median and/or mean and extreme values were reported for continuous variables.

Univariate analyses were performed using Student's t-test, as appropriate, for comparing quantitative variables (in particular delays) between groups for normally distributed data. Analysis of variance (ANOVA) was used to compare quantitative variables among multiple groups. Survival after transplantation was calculated using the Kaplan–Meier method and the log-rank test was used to analyze differences in survival.

RESULTS

Thirty patients underwent LT between 01/01/1994 and 12/31/2017 for iatrogenic BDI (Table

1) across 11 expert French LT centers. This represents 0.13% of the total workload of LTs

(23 329) performed over the duration of the study. Twenty-three of BDIs (76.7%) occurred after 1990, with 21 LTs (70%) carried out between 2006 and 2017. The trend in LT for BDI relative to total LT in this period is presented in Figure 1.

Nineteen patients were females (63.3%), and the median age at cholecystectomy was 40 [range 9-66]. The median age at LT was 52 [range 22-68]. Pre-existing hepatic disease was absent in all patient at the time of index BDI. The indications for cholecystectomy were symptomatic gallbladder stones in ten cases (33.3%), acute cholecystitis in nine cases (30%), common bile duct lithiasis in one case (3.3%), biliary pancreatitis in two cases (6.7%), and unknown in eight cases (26.7%). In twenty (66.7%) patients the BDI occurred during a laparoscopic cholecystectomy.

Presentation of iatrogenic BDI included; biliary sepsis (seven cases), bile leak (seven cases), cholestatic jaundice (five cases), upper gastrointestinal bleeding (one case), or secondary biliary cirrhosis (one case) (Table 2). The exact clinical presentation was unknown

in nine patients (30%). The median time to diagnosis of BDI was 15 days post cholecystectomy, with four cases diagnosed during surgery, thirteen in the first 15 postoperative days, and nine after 15 days post-cholecystectomy. Time of diagnosis was unknown for the remaining four patients. The period before diagnosis was not recorded in the medical files for four of patients. According to Strasberg classification, the types of BDI included B (one case), C (one case), D (six cases), E1 (three cases), E2 (six cases), E3 (three cases), E4 (five cases), and non-classifiable (five cases). Eleven patients (36.6%) had an associated vascular injury : 10 injuries of the right hepatic artery, including one associated with a portal vein injury, 1 injury of the common hepatic artery.

Twenty-five cases of BDI (83.4%) occurred in non-expert centers, and 20 of them (80%) were initially treated in these centers. The average time between BDI and treatment was 24 months (range 0,23-108) (Table 3). The average number of surgeries per patient before LT was 2.5 ± 1.13 . Thirteen (43.3%) patients required endoscopy/ERCP, and a biliary stent was used in 4 cases (30.8%). Fourteen (46.7%) patients required interventional radiology, with a biliary drain performed in eleven patients (78.6%), and a Transjugular Intrahepatic Portosystemic Shunt (TIPS) performed in three patients (21.4%). Eleven hepatico-jejunal anastomoses were initially performed; nine of them (81.8%) were complicated by stenosis. The median time interval between BDI and enrolment onto the LT waiting list was 8.5 years (range 0.2-32) (Table 4). The median waiting list duration was 3 months (range 0.1-116). The median time between BDI and LT was 10 years (range 0.2-32). Median MELD-score at LT was 16 (range 6-40). Eight patients (26.7%) required an expert component to access LT, with a median MELD-score of 8; the median time between expert component and LT was 2 months (range 0.1-6.5). Three LTs were performed as emergencies (in less than 7 days after list inscription).

The median time between BDI and LT was 3 years (range 0.2-18) with associated vascular lesion, versus 11.7 years (range 6-32) without vascular lesion ($p=0.006$). It was 42.5

months (range 9-136) if BDI occurred in an expert center, versus 144 months (range 2-384) in a non-expert center ($p=0.03$).

The indications for LT included chronic liver failure (fourteen patients), uncontrolled biliary sepsis (six patients), uncontrolled portal hypertension (five patients), biliovascular destruction (three patients), acute liver failure (one patient), and refractory pruritus (one patient).

The median follow-up period was 6.1 years (range 0-16) after LT. Morbidity was 86.7% (Table 5), including severe complications in 80% of cases (Clavien-Dindo \geq III). Two patients (6.7%) required re-transplantation for extended biliary necrosis (1 patient) and secondary biliary cirrhosis (1 patient). Graft survival was 76% at 3 months, 73% at 1 year, and 69% at 5 years (Table 6). Patient survival was 80% at 3 months, and 76.5% at 1 year and 5 years. The survival curves for grafts and patients are shown in Figure 2.

Mortality post-LT was 23.5% (seven patients). The causes of death included hemorrhagic shock (three patients), septic shock (one patient), mesenteric ischemia (one patient), and unknown for the remaining two patients.

DISCUSSION

We present a comprehensive review of liver transplantations for BDI following cholecystectomy in France. There are a number of case studies that have been reported in the current literature documenting outcomes in this cohort of patients (8,3,9–12), with a small number of multicenter studies available (Spain : 25 cases (13), Argentina : 18 cases (14), United States : 61 LT (15)). Indeed, BDI accounts for a very small percentage of workload for liver transplantation, however, it remains a major concern in the field of hepatobiliary surgery. Iatrogenic BDI is a relatively rare, but serious complication of cholecystectomy, often occurring in young patients initially operated on for a benign disease(16), with potentially life changing consequences (17). The incidence of BDI in laparoscopic cholecystectomy has plateaued to 0.6% since its inception (18), however, the severity of BDI associated with

laparoscopic surgery is greater than that associated with open cholecystectomy (8). This is most likely to be due to the underlying mechanism of the injury, the associated vascular injuries(6,19) and, sometimes, the requirement for multiple surgical procedures to repair the injury.

In our series, twenty BDI were identified following laparoscopic cholecystectomy, with associated vascular injuries in eleven cases. The incidence of LT for BDI in France is increasing, compared to other parts of the world (13). However, this is not associated with a concurrent rise in the rate of BDI, and is likely to reflect the increase in the inappropriate management of BDI(22). Similar to published evidence, our study supports the observation that LT in iatrogenic BDI is reserved for patients presenting with late complications of secondary biliary cirrhosis, including sepsis, jaundice, portal hypertension or refractory pruritus. The time interval between BDI and the LT is very long (3 years in the case of vascular lesions and 11.7 years without), which reflects its indication being reserved for long-term sequelae of BDI. Furthermore, LT is considered to be a final resort, following multiple procedures (surgery, endoscopy +/- interventional radiology (23)). In severe BDI (Strasberg E in 56% of the cases), it is likely that the indication for LT was due to inappropriate repair carried out under poor conditions and/or by non-experts centers in 87% of cases (22). It is therefore essential that all BDI cases (> or = Strasberg B) are managed appropriately in expert hepatobiliary centers. In the current era, in which surgeons are often more experienced with laparoscopy than open surgery, it may be preferable to refer bile duct injury patients to an appropriate institution than to convert them to open surgery or re-operate.

With respect to the outcomes of LT for BDI, we confirmed the results of previous studies showing a high mortality rate (23%), which was much higher than for other indications (i.e., UNOS data (15)). We also identified severe morbidity (Dindo >2) at a rate of 80%. This is likely due to the technically challenging nature of in this setting, with operative difficulties and massive bleeding frequently encountered due to portal hypertension, abdominal adhesions, biliary infection with resistant bacteria, liver abscesses, and previous vascular injuries with cavernous vessels. These factors are likely to contribute to the high rates

of operative mortality and post-operative complications such as artery thrombosis (5/30) and infections (23/30).

Patients with low MELD scores remained on the waiting list for a long time and were transplanted under sub-optimal conditions, with severe malnutrition due to chronic sepsis or jaundice. Access to LT for such patients is a serious issue. The present study included only patients for whom transplantation was carried out, not those who died while on the waiting list. In the literature, up to 20% of the patients listed for BDI died while on the waiting list(20,21). Access to grafts is typically straightforward for patients with acute liver failure caused by mixed injuries; however, such cases are rare, and most patients on waiting lists suffer from chronic liver disease and have a median MELD score of 16. Among these patients, the indications included recurrent cholangitis, symptomatic hypertension or refractory pruritus rather than hepatic failure. We highly recommend that patients with iatrogenic disease may benefit from being prioritized for special consideration by national regulatory agencies, so that they can be optimally prepared (e.g., in terms of nutrition and biliary / abscess drainage) and transplanted as soon as possible.

Specific surgical and medical considerations should be made in the management of these patients, such as the use of extracorporeal venous bypass in cases of severe portal hypertension, reduction of post-LT immunosuppression in infected patients, and intensive post-operative renutrition from jejunostomy.

Although the post-operative risks were high, the long-term results of LT were relatively positive, with a five-year survival of rate 70%, showing that LT is the only effective treatment for severe BDI .

In conclusion, LT is the last and only option for severe BDI and for the sequelae of BDI management including secondary biliary cirrhosis or recurrent untreatable cholangitis. These difficult transplantations, which are fortunately rare in France and worldwide, are associated with good long-term results but high morbidity and mortality, as well as a 6.7% rate of re-transplantation, mainly linked to sepsis and vascular complications.

To improve upon these short-term results, it is necessary to facilitate access to liver grafts to avoid death on the waiting list and provide patients with LT at an optimal time. Furthermore, LT should be performed by experienced transplant surgeons and anesthesiologists because of the unique operative management requirements for these patients.

The English in this document has been checked by at least two professional editors, both native speakers of English

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Figure 1: Number of liver transplantations for iatrogenic bile duct injury, with corresponding number of bile duct injuries among all liver transplantations in the study period.

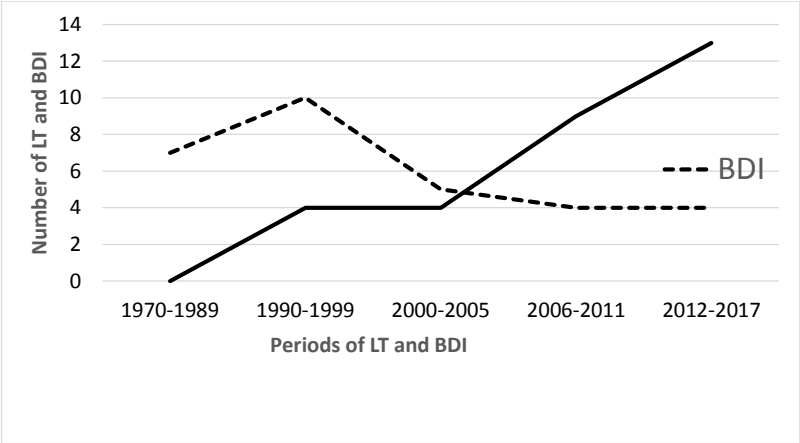


Figure 2: Kaplan-Meier plots of graft and patient survival after liver transplantation for iatrogenic bile duct injury. The survival curves did not significantly differ ($p = 0.586$).

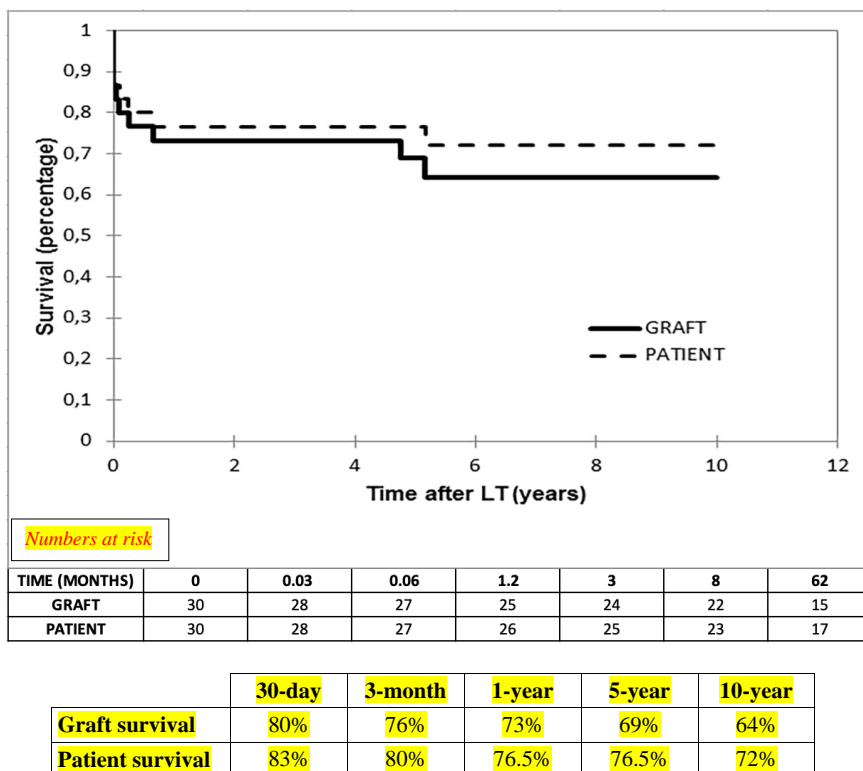


Table 1: Patient demographics and characteristics.

Patient characteristics	All patients (n = 30)
Sex ratio (M/F)	11/19
Median age at BDI (years)	40 (9 - 66)
Median age at LT (years)	52 (22 - 68)
Indication of cholecystectomy	
Symptomatic gallbladder	10 (33.3%)
stones Acute cholecystitis	9 (30%)
Common bile duct lithiasis	1 (3.3%)
Biliary pancreatitis	2 (6.7%)
NR	8 (26.7%)
Surgical approach	
Laparoscopy	20 (66.7%)
Laparotomy	10 (33.3%)

M: Male; F: Female; BDI: Bile Duct Injury; LT: Liver Transplantation; NR: Not Reported

Table 2: Diagnosis and type of iatrogenic bile duct injury.

Diagnosis of BDI	All patients (n = 30)
Clinic presentation	
Biliary sepsis	7 (23.5%)
Bile leak	7 (23.3%)
Cholestatic jaundice	5 (16.6%)
Upper gastrointestinal bleeding	1 (3.3%)
Secondary biliary cirrhosis	1 (3.3%)
NR	9 (30%)
Median diagnostic delay (days)	15 (0 - 9855)
intra-operative	4 (13.3%)
early post-operative (< 15 days)	13 (43.4%)
late post-operative (> 15 days)	9 (30%)
NR	4 (13.3%)
Strasberg classification	
B	1 (3.3%)
C	1 (3.3%)
D	6 (20%)
E1	3 (10%)
E2	6 (20%)
E3	3 (10%)
E4	5 (16.7%)
NR	5 (16.7%)
Associated vascular injury	11 (36.6%)
RHA	9 (81.8%)
CHA	1 (9.1%)
RHA + PV	1 (9.1%)

BDI: Bile Duct Injury; NR: Not Reported; RHA: Right Hepatic Artery; CHA: Common Hepatic Artery; PV: Portal Vein

Table 3: Initial procedures for treatment of iatrogenic bile duct injury.

Treatment of BDI	All patients (n = 30)
Average time between BDI and initial treatment	24 months
Average number of surgeries per patient before LT	2.5 (1 - 6)
Endoscopy/ERCP	13 (43.3%)
Biliary stent	4 (30.8%)
Average number per patient	1.8 (0 - 4)
Interventional radiology	14 (46.7%)
Biliary drain	11 (78.6%)
TIPS	3 (21.4%)
Primary hepatico-jejunal anastomosis	11 (36.7%)
Anastomotic stenosis	9 (81.8%)
Expert center	
yes	10 (33.3%)
no	20 (66.7%)

BDI: Bile Duct Injury; ERCP: Endoscopic Retrograde Cholangiopancreatography; LT: Liver Transplantation; TIPS: Transjugular Intrahepatic Portosystemic Shunt

Table 4: Liver Transplantation for iatrogenic bile duct injury : general summary.

Liver Transplantation	All patients (n = 30)	
Median age (years)	52 (22 - 68)	
Median time BDI / list inscription (years)	8.5 (0.14 - 32)	
Median duration on waiting list (months)	3 (0.03 - 45.8)	
Median time BDI / LT (years)	10 (0.2 - 32)	
Associated vascular lesion (years)	3	p = 0.006
No associated vascular lesion (years)	11.7	
BDI in an expert center (months)	42.5	p = 0.03
BDI in a non-expert center (months)	144	
Median MELD-score	16 (6 - 40)	
Expert component	8 (26.7%)	
Uncontrolled biliary sepsis	4 (13.4%)	
Refractory pruritus	1 (3.3%)	
Biliovascular destruction	3 (10%)	
Median MELD-score	8 (6 - 18)	
Median time expert component / LT (months)	2 (0.1 - 6.5)	
Indications of LT		
Chronic liver failure	14 (46.7%)	
Uncontrolled biliary sepsis	6 (20%)	
Uncontrolled portal hypertension	5 (16.7%)	
Biliovascular destruction	3 (10%)	
Acute liver failure	1 (3.3%)	
Refractory pruritus	1 (3.3%)	
Portal hypertension	19 (63.3%)	

BDI: Bile Duct Injury; MELD: Model for End Stage Liver Disease; LT: Liver Transplantation

Table 5: Morbidity and mortality of liver transplantation for iatrogenic bile duct injury.

Morbi-mortality after LT	All patients (n = 30)	Clavien-Dindo
Immunologic complications	8	
Acute rejection	7	2
autoimmune hepatitis	1	2
Vascular complications	10	
Hepatic artery thrombosis	5	2 – 3
Ischemic cholangiopathy	2	2
Pulmonary embolism	1	2
Mesenteric ischemia	1	5
Stenosis of the arterial anastomosis	1	2
Hemorrhagic complications	9	
Abdominal wall hematoma	2	2
Hemoperitoneum	2	3
Hemorrhagic shock	3	3 – 5
Hemothorax	1	3
Cerebral hematoma	1	2
Infectious complications	23	
Infectious cholangitis	5	2
Septic shock	4	4
Pulmonary infection	3	2
Herpetic stomatitis	2	2
Intra-abdominal abscess	2	3
Peritonitis	2	3
Biliary fistulae	2	3
Acute pyelonephritis	1	2
Acute CMV hepatitis	1	2
Ascites fluid infection	1	2
Parietal complications	3	
Incisional hernia	2	2
Strangled eventration	1	3
Other complications	11	
Acute renal failure	4	4
Pneumothorax	1	3
Myoclonic encephalopathy	2	2
Stenosis of the hepatico-jejunal anastomosis	1	3
Bedsore	1	2
Duodenal ulcer	1	2
Portal hypertension	1	2
	26 patients (86.7%)	24 patients ≥ III (80%)

LT: Liver Transplantation; CMV: cytomegalovirus

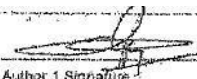

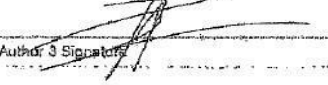



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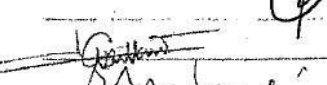
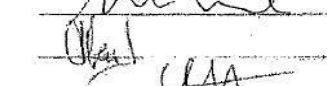

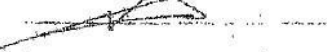



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☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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
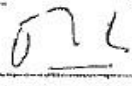




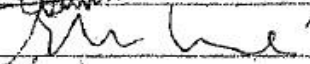
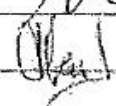
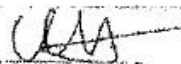
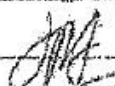

Space for additional information if required:

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